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(54) Title: NOVEL COMPOUNDS

(57) Abstract: MPROT45 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing MPROT45 polypeptides and polynucleotides in diagnostic assays.

Description of the Invention

In a first aspect, the present invention relates to MPROT45 polypeptides. Such polypeptides include:

- (a) an isolated polypeptide encoded by a polynucleotide comprising the sequence of SEQ ID NO:1;
- 5 (b) an isolated polypeptide comprising a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to the polypeptide sequence of SEQ ID NO:2;
- (c) an isolated polypeptide comprising the polypeptide sequence of SEQ ID NO:2;
- 10 (d) an isolated polypeptide having at least 95%, 96%, 97%, 98%, or 99% identity to the polypeptide sequence of SEQ ID NO:2;
- (e) the polypeptide sequence of SEQ ID NO:2; and
- 15 (f) an isolated polypeptide having or comprising a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to the polypeptide sequence of SEQ ID NO:2;
- (g) fragments and variants of such polypeptides in (a) to (f).

Polypeptides of the present invention are believed to be members of the Matrix Metalloproteinases family of polypeptides. They are therefore of interest because all types of proteases can play critical roles in disease pathology. Therefore designing or screening for selective protease antagonists or agonists can lead to the development of new drugs (Seife, C., Science 277, 1602-1603).

The biological properties of the MPROT45 are hereinafter referred to as "biological activity of MPROT45" or "MPROT45 activity". Preferably, a polypeptide of the present invention exhibits at least one biological activity of MPROT45.

Polypeptides of the present invention also includes variants of the aforementioned polypeptides, including all allelic forms and splice variants. Such polypeptides vary from the reference polypeptide by insertions, deletions, and substitutions that may be conservative or non-conservative, or any combination thereof. Particularly preferred variants are those in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acids are inserted, substituted, or deleted, in any combination.

Preferred fragments of polypeptides of the present invention include an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids from the amino acid sequence of SEQ ID NO: 2, or an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids truncated or deleted from the amino acid sequence of SEQ ID NO: 2. Preferred fragments are biologically active fragments that mediate the biological activity of MPROT45,

including those with a similar activity or an improved activity, or with a decreased undesirable activity. Also preferred are those fragments that are antigenic or immunogenic in an animal, especially in a human.

Fragments of the polypeptides of the invention may be employed for producing
5 the corresponding full-length polypeptide by peptide synthesis; therefore, these variants may be employed as intermediates for producing the full-length polypeptides of the invention. The polypeptides of the present invention may be in the form of the "mature" protein or may be a part of a larger protein such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence that contains secretory
10 or leader sequences, pro-sequences, sequences that aid in purification, for instance multiple histidine residues, or an additional sequence for stability during recombinant production.

Polypeptides of the present invention can be prepared in any suitable manner, for instance by isolation from naturally occurring sources, from genetically engineered host cells
15 comprising expression systems (*vide infra*) or by chemical synthesis, using for instance automated peptide synthesizers, or a combination of such methods. Means for preparing such polypeptides are well understood in the art.

In a further aspect, the present invention relates to MPROT45 polynucleotides.

Such polynucleotides include:

- 20 (a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to the polynucleotide sequence of SEQ ID NO:1;
- (b) an isolated polynucleotide comprising the polynucleotide of SEQ ID NO:1;
- (c) an isolated polynucleotide having at least 95%, 96%, 97%, 98%, or 99% identity to the polynucleotide of SEQ ID NO:1;
- 25 (d) the isolated polynucleotide of SEQ ID NO:1;
- (e) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to the polypeptide sequence of SEQ ID NO:2;
- (f) an isolated polynucleotide comprising a polynucleotide sequence encoding the
30 polypeptide of SEQ ID NO:2;
- (g) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to the polypeptide sequence of SEQ ID NO:2;
- (h) an isolated polynucleotide encoding the polypeptide of SEQ ID NO:2;

(i) an isolated polynucleotide having or comprising a polynucleotide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to the polynucleotide sequence of SEQ ID NO:1;

(j) an isolated polynucleotide having or comprising a polynucleotide sequence encoding a 5 polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to the polypeptide sequence of SEQ ID NO:2; and polynucleotides that are fragments and variants of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.

10 Preferred fragments of polynucleotides of the present invention include an isolated polynucleotide comprising an nucleotide sequence having at least 15, 30, 50 or 100 contiguous nucleotides from the sequence of SEQ ID NO: 1, or an isolated polynucleotide comprising an sequence having at least 30, 50 or 100 contiguous nucleotides truncated or deleted from the sequence of SEQ ID NO: 1.

15 Preferred variants of polynucleotides of the present invention include splice variants, allelic variants, and polymorphisms, including polynucleotides having one or more single nucleotide polymorphisms (SNPs).

20 Polynucleotides of the present invention also include polynucleotides encoding polypeptide variants that comprise the amino acid sequence of SEQ ID NO:2 and in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acid residues are substituted, deleted or added, in any combination.

25 In a further aspect, the present invention provides polynucleotides that are RNA transcripts of the DNA sequences of the present invention. Accordingly, there is provided an RNA polynucleotide that:

- (a) comprises an RNA transcript of the DNA sequence encoding the polypeptide of SEQ ID NO:2;
- (b) is the RNA transcript of the DNA sequence encoding the polypeptide of SEQ ID NO:2;
- 30 (c) comprises an RNA transcript of the DNA sequence of SEQ ID NO:1; or
- (d) is the RNA transcript of the DNA sequence of SEQ ID NO:1; and RNA polynucleotides that are complementary thereto.

The polynucleotide sequence of SEQ ID NO:1 shows homology with Matrix Metalloproteinase 19 (Cossins et al., Biochem. Biophys. Res. Commun. 228(2), 494-498, 35 1996). The polynucleotide sequence of SEQ ID NO:1 is a cDNA sequence that encodes the polypeptide of SEQ ID NO:2. The polynucleotide sequence encoding the polypeptide of

SEQ ID NO:2 may be identical to the polypeptide encoding sequence of SEQ ID NO:1 or it may be a sequence other than SEQ ID NO:1, which, as a result of the redundancy (degeneracy) of the genetic code, also encodes the polypeptide of SEQ ID NO:2. The polypeptide of the SEQ ID NO:2 is related to other proteins of the Matrix Metalloproteinases 5 family, having homology and/or structural similarity with Matrix Metalloproteinase 19 (Cossins et al., Biochem. Biophys. Res. Commun. 228(2). 494-498, 1996).

Preferred polypeptides and polynucleotides of the present invention are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore, preferred polypeptides and polynucleotides of the present 10 invention have at least one MPROT45 activity.

Polynucleotides of the present invention may be obtained using standard cloning and screening techniques from a cDNA library derived from mRNA in cells of human colon, brain and testis, (see for instance, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). 15 Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

When polynucleotides of the present invention are used for the recombinant production of polypeptides of the present invention, the polynucleotide may include the 20 coding sequence for the mature polypeptide, by itself, or the coding sequence for the mature polypeptide in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence that facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the 25 invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, Proc Natl Acad Sci USA (1989) 86:821-824, or is an HA tag. The polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

30 Polynucleotides that are identical, or have sufficient identity to a polynucleotide sequence of SEQ ID NO:1, may be used as hybridization probes for cDNA and genomic DNA or as primers for a nucleic acid amplification reaction (for instance, PCR). Such probes and primers may be used to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other 35 genes (including genes encoding paralogs from human sources and orthologs and paralogs from species other than human) that have a high sequence similarity to SEQ ID NO:1,

polypeptide in a host may be used. The appropriate polynucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, (*ibid*). Appropriate secretion signals may be incorporated into the desired polypeptide to allow secretion of the translated protein 5 into the lumen of the endoplasmic reticulum, the periplasmic space or the extracellular environment. These signals may be endogenous to the polypeptide or they may be heterologous signals.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. 10 In this event, the cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from 15 recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques 20 for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation and/or purification.

Polynucleotides of the present invention may be used as diagnostic reagents, through detecting mutations in the associated gene. Detection of a mutated form of the gene characterized by the polynucleotide of SEQ ID NO:1 in the cDNA or genomic sequence and 25 which is associated with a dysfunction will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered spatial or temporal expression of the gene.

Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques well known in the art.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from 30 blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for detection or it may be amplified enzymatically by using PCR, preferably RT-PCR, or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the 35 amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled MPROT45 nucleotide sequences. Perfectly

matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence difference may also be detected by alterations in the electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (see, for instance, Myers *et al.*, *Science* 5 (1985) 230:1242). Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton *et al.*, *Proc Natl Acad Sci USA* (1985) 85: 4397-4401).

An array of oligonucleotides probes comprising MPROT45 polynucleotide sequence or fragments thereof can be constructed to conduct efficient screening of e.g., 10 genetic mutations. Such arrays are preferably high density arrays or grids. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability, see, for example, M. Chee *et al.*, *Science*, 274, 610-613 (1996) and other references cited therein.

15 Detection of abnormally decreased or increased levels of polypeptide or mRNA expression may also be used for diagnosing or determining susceptibility of a subject to a disease of the invention. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of 20 polynucleotides, such as, for example, nucleic acid amplification, for instance PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radio-immunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

25 Thus in another aspect, the present invention relates to a diagnostic kit comprising:
(a) a polynucleotide of the present invention, preferably the nucleotide sequence of SEQ ID NO: 1, or a fragment or an RNA transcript thereof;
(b) a nucleotide sequence complementary to that of (a);
30 (c) a polypeptide of the present invention, preferably the polypeptide of SEQ ID NO:2 or a fragment thereof; or
(d) an antibody to a polypeptide of the present invention, preferably to the polypeptide of SEQ ID NO:2.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a 35 substantial component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, particularly diseases of the invention, amongst others.

SEQUENCE INFORMATION

SEQ ID NO:1

>

ATGGTCGCGCGTCCGCCTCTGCTGCGGCCCTGCAGCTGCTACTGTGGGCCACCTG
 5 GACGCCAGCCCGGGAGCGCGGAGGCCAGGAGCTGCGCAAGGAGGCGGAGGCATTCTA
 GAGAACTACGGATACTCAATGAACAGGTCCCCAAAGCTCCACCTCCACTCGATTCA
 GATGCCATCAGAGCGTTCACTGGGTGTCAGCTACCTGTCAGCGCGTGTGGACC
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 15 GATGAGCGCTGGTCCCTGAGCCGCCGCCGCCGCAACCTGTTCTGG
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 ATGATGGAGATTCTACTCTTCAAAGGGGTCGATGCTGGAGG
 25 CCCCTCTTCTCCCTCTCGCGCCCTCATCCTCTCAAGGG
 CTGGGGCGAGGGGACTGCAAGTGGAGCC
 TACTACCCCGAAGTCTGCGAGGACTGGCAG
 GGCATCCCTGAGGAGGTCA
 CGAGATGACCGCTACTGGGCC
 TGGGCCACCGAGCTGCC
 30 TGA

SEQ ID NO:2

>

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 LRQMTRPRCGVTDTNSYAA
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 FVVL
 AH
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 GGS
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 VLARG
 GLQ
 VE
 PY
 PRSL
 QDW
 WGGI
 PEE
 VSG
 GAL
 PRPD
 GSII
 FF
 RDDRY
 WRLD
 QAKL
 QATT
 SGR
 WATE
 LPWM
 GCH
 WHAN
 SG
 ALF

Claims

1. An isolated polypeptide selected from the group consisting of:
 - (a) an isolated polypeptide encoded by a polynucleotide comprising the sequence of SEQ ID NO:1;
 - (b) an isolated polypeptide comprising a polypeptide sequence having at least 95% identity to the polypeptide sequence of SEQ ID NO:2;
 - (c) an isolated polypeptide having at least 95% identity to the polypeptide sequence of SEQ ID NO:2; and
 - (d) fragments and variants of such polypeptides in (a) to (e).
2. The isolated polypeptide as claimed in claim 1 comprising the polypeptide sequence of SEQ ID NO:2.
3. The isolated polypeptide as claimed in claim 1 which is the polypeptide sequence of SEQ ID NO:2.
4. An isolated polynucleotide selected from the group consisting of:
 - (a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95% identity to the polynucleotide sequence of SEQ ID NO:1;
 - (b) an isolated polynucleotide having at least 95% identity to the polynucleotide of SEQ ID NO:1;
 - (c) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95% identity to the polypeptide sequence of SEQ ID NO:2;
 - (d) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95% identity to the polypeptide sequence of SEQ ID NO:2;
 - (e) an isolated polynucleotide with a nucleotide sequence of at least 100 nucleotides obtained by screening a library under stringent hybridization conditions with a labeled probe having the sequence of SEQ ID NO: 1 or a fragment thereof having at least 15 nucleotides;
 - (f) a polynucleotide which is the RNA equivalent of a polynucleotide of (a) to (e); or a polynucleotide sequence complementary to said isolated polynucleotide and polynucleotides that are variants and fragments of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.
5. An isolated polynucleotide as claimed in claim 4 selected from the group consisting of:

35

- (a) an isolated polynucleotide comprising the polynucleotide of SEQ ID NO:1;
- (b) the isolated polynucleotide of SEQ ID NO:1;
- (c) an isolated polynucleotide comprising a polynucleotide sequence encoding the polypeptide of SEQ ID NO:2; and

5 (d) an isolated polynucleotide encoding the polypeptide of SEQ ID NO:2.

6. An expression system comprising a polynucleotide capable of producing a polypeptide of claim 1 when said expression vector is present in a compatible host cell.

10 7. A recombinant host cell comprising the expression vector of claim 6 or a membrane thereof expressing the polypeptide of claim 1.

15 8. A process for producing a polypeptide of claim 1 comprising the step of culturing a host cell as defined in claim 7 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture medium.

9. An antibody immunospecific for the polypeptide of any one of claims 1 to 3.

10. A method for screening to identify compounds that stimulate or inhibit the function or level of the polypeptide of claim 1 comprising a method selected from the group consisting of:

20 (a) measuring or, detecting, quantitatively or qualitatively, the binding of a candidate compound to the polypeptide (or to the cells or membranes expressing the polypeptide) or a fusion protein thereof by means of a label directly or indirectly associated with the candidate compound;

25 (b) measuring the competition of binding of a candidate compound to the polypeptide (or to the cells or membranes expressing the polypeptide) or a fusion protein thereof in the presence of a labeled competitor;

30 (c) testing whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide, using detection systems appropriate to the cells or cell membranes expressing the polypeptide;

35 (d) mixing a candidate compound with a solution containing a polypeptide of claim 1, to form a mixture, measuring activity of the polypeptide in the mixture, and comparing the activity of the mixture to a control mixture which contains no candidate compound; or

 (e) detecting the effect of a candidate compound on the production of mRNA encoding said polypeptide or said polypeptide in cells, using for instance, an ELISA assay.

SEQUENCE LISTING

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